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Imazalil and Imazalil Sulfate
Interim Registration Review Decision
Case Number 2325

March 2021

Approved by: _____

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I. INTRODUCTION

This document is the Environmental Protection Agency's (EPA or the Agency) Interim Registration Review Decision (ID) for imazalil and imazalil sulfate (hereafter referred to collectively as imazalil) (PC Code 111901 (imazalil) and 111902 (imazalil sulfate), case 2325), and is being issued pursuant to 40 CFR §§ 155.56 and 155.58. A registration review decision is the Agency's determination whether a pesticide continues to meet, or does not meet, the standard for registration in the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). The Agency may issue, when it determines it to be appropriate, an interim registration review decision before completing a registration review. Among other things, the interim registration review decision may determine that new risk mitigation measures are necessary, lay out interim risk mitigation measures, identify data or information required to complete the review, and include schedules for submitting the required data, conducting the new risk assessment and completing the registration review. Additional information on imazalil can be found in the EPA's public docket (EPA-HQ-OPP-2013-0305) at www.regulations.gov.

FIFRA, as amended by the Food Quality Protection Act (FQPA) of 1996, mandates the continuous review of existing pesticides. All pesticides distributed or sold in the United States must be registered by the EPA based on scientific data showing that they will not cause unreasonable risks to human health or to the environment when used as directed on product labeling. The registration review program is intended to make sure that, as the ability to assess and reduce risk evolves and as policies and practices change, all registered pesticides continue to meet the statutory standard of no unreasonable adverse effects. Changes in science, public policy, and pesticide use practices will occur over time. Through the registration review program, the Agency periodically re-evaluates pesticides to make sure that as these changes occur, products in the marketplace can continue to be used safely. Information on this program is provided at http://www.epa.gov/pesticide-reevaluation. In 2006, the Agency implemented the registration review program pursuant to FIFRA § 3(g) and will review each registered pesticide every 15 years to determine whether it continues to meet the FIFRA standard for registration.

EPA is issuing an ID for imazalil so that it can (1) move forward with aspects of the registration review that are complete and (2) implement interim risk mitigation (see [Appendices A and B]). The Agency is currently working with the U.S. Fish and Wildlife Service and the National Marine Fisheries Service (collectively referred to as, "the Services") to improve the consultation process for national threatened and endangered (listed) species for pesticides in accordance with the Endangered Species Act (ESA) § 7. Therefore, although EPA has not yet fully evaluated risks to federally-listed species, the Agency will complete its listed species assessment and any necessary consultation with the Services for imazalil prior to completing the imazalil registration review. Likewise, the Agency will complete endocrine screening for imazalil, pursuant to the Federal Food, Drug, and Cosmetic Act (FFDCA) § 408(p), before completing registration review. See the Proposed Interim Decision (PID) for additional information on the listed species assessment and the endocrine screening for the imazalil registration review.

Imazalil is a systemic imidazole fungicide with products registered for control of a variety of fungal pathogens. Products containing imazalil were first registered in 1983 and were subject to

reregistration, which was completed in 2003. Conventional products containing imazalil and imazalil sulfate are used for postharvest treatment of citrus fruits and bananas (import tolerance only). Conventional products containing imazalil and imazalil sulfate were registered for seed treatment and ornamental uses at the beginning of this registration review; however, these uses have since been cancelled or products have been amended to terminate the uses. Products containing imazalil are also used as antimicrobial pesticides to prevent outbreaks of *Aspergillus* spp. (especially *A. fumigatus*) in egg hatchery facilities and equipment. There are no registered residential uses for imazalil.

This document is organized in five sections: the Introduction, which includes this summary and a summary of public comments and the EPA's responses; Use and Usage, which describes how and why imazalil is used and summarizes data on its use; Scientific Assessments, which summarizes the EPA's risk and benefits assessments, updates or revisions to previous risk assessments, and provides broader context with a discussion of risk characterization; the Interim Registration Review Decision, which describes the mitigation measures required to address risks of concern and the regulatory rationale for the EPA's ID; and, lastly, the Next Steps and Timeline for completion of this registration review.

A. Updates Since the Proposed Interim Decision was Issued

In June 2019, the EPA published the PID for imazalil. In this ID, there is one update to what was proposed in the PID. Several comments were received on the PID as well as a new study on actual post-harvest citrus use of products containing imazalil. Due to this new information and the resulting changes to the risk estimates, mitigation proposed in the PID for conventional uses has been revised. The Agency is no longer requiring closed mixing/loading systems for post-harvest applications to citrus. No changes have been made to mitigation of antimicrobial uses. Please see § I.B, § III.A.1, and § IV.A for additional information.

B. Summary of Imazalil Registration Review

Pursuant to 40 CFR § 155.50, the EPA formally initiated registration review for imazalil and imazalil sulfate with the opening of the registration review docket for the case. The following summary highlights the docket opening and other significant milestones that have occurred thus far during the registration review of imazalil and imazalil sulfate.

- December 2013 - The *Imazalil and Imazalil Sulfate Preliminary Work Plan* (PWP*)*, *Imazalil and Imazalil Sulfate: Human Health Assessment Scoping Document in Support of Registration Review*, and *Registration Review - Preliminary Problem Formulation for Ecological Risk and Environmental Fate, Endangered Species, and Drinking Water Assessments for Imazalil and Imazalil Sulfate* were posted to the docket for a 60-day public comment period.

- July 2014 - The *Final Work Plan* (FWP) and the *Revised Preliminary Problem Formulation for Ecological Risk and Environmental Fate, Endangered Species, and*

Drinking Water Assessments for Imazalil and Imazalil Sulfate for imazalil and imazalil sulfate were issued. The comments received in response to the PWP did not change the regulatory timeline, the planned ecological and human health risk assessment needs, or anticipated data requirements for imazalil.

- November 2014 - The Generic Data Call-Ins (GDCI) for imazalil and imazalil sulfate were issued for data needed to conduct the registration review risk assessments. The GDCIs were satisfied.

- November 2018 - The Agency announced the availability of *Imazalil and Imazalil Sulfate: Preliminary Ecological Risk Assessment for Registration Review* and *Imazalil and Imazalil Sulfate Human Health Draft Risk Assessment for Registration Review* for a 60-day public comment period. Six comments were received concerning the draft risk assessments (DRAs).

- July 2019 - The Agency announced the availability of the *Imazalil and Imazalil Sulfate: Proposed Interim Decision*, for a 60-day public comment period. Five comments were received concerning the PID. These comments and the Agency's responses are summarized below. The comments did change the risk conclusions and registration review timeline for imazalil. Along with the PID, the following documents were also posted to the imazalil and imazalil sulfate docket:
    - *Imazalil and Imazalil Sulfate. HED Response to Public Comments on the Imazalil and Imazalil Sulfate Draft Risk Assessment for Registration Review* – dated June 19, 2019
    - *Use, Usage, Benefits, and Impact of Potential Mitigation on Imazalil (PC# 111901) and Imazalil Sulfate (PC# 111902) Post-harvest Treatment of Citrus* – dated June 28, 2019

- March 2021 – The Agency completed the ID and posted the ID in the docket for imazalil and imazalil sulfate. Along with the ID, the following documents are also being posted to the docket:
    - *Imazalil: Updated Occupational Handler and Post Application Risk Estimates Re-evaluating Post-Harvest Treatment Equipment to Support Registration Review* – dated February 8, 2021
    - *Imazalil and Imazalil Sulfate Usage in Citrus Packing Houses in California* – dated May 28, 2020
    - *Imazalil: Addendum to the Human Health Draft Risk Assessment for Registration Review* – dated 3/24/2021.

C. Summary of Public Comments on the Proposed Interim Decision and Agency Responses

During the 60-day public comment period for the PID, which opened on July 31, 2019 and closed on September 30, 2019, the Agency received public comments from eight sources. Comments were submitted by California Citrus Quality Council (CCQC), Environmental

Working Group (EWG), multiple packinghouses and supply companies, United States Department of Agriculture (USDA), University of California, and the Imazalil Task Force (represented by technical registrants, Janssen PMP, a Division of Janssen Pharmaceutica NV (Janssen) and ADAMA Agricultural Solutions Ltd. (ADAMA)). One comment by USDA addressed antimicrobial uses. Substantive comments, comments of a broader regulatory nature, and the Agency's responses to those comments are summarized below. The Agency thanks all commenters for their comments and has considered them in developing this ID.

Comments Submitted by California Citrus Quality Council (CCQC) (Docket ID: EPA-HQ-OPP-2013-0305-0055), United States Department of Agriculture (USDA) (Docket ID: EPA-HQ-OPP-2013-0305-0049), Imazalil Task Force (Docket ID: EPA-HQ-OPP-2013-0305-0048), University of California, Riverside (Docket ID: EPA-HQ-OPP-2013-0305-0054), Cecelia Packing Corporation (Docket ID: EPA-HQ-OPP-2013-0305-0050), Haury Inc. (Docket ID: EPA-HQ-OPP-2013-0305-0051), Sun Pacific (Docket ID: EPA-HQ-OPP-2013-0305-0052), Johnston Farms (Docket ID: EPA-HQ-OPP-2013-0305-0053), and Fruit Growers Supply and other packing houses and supply companies (FGS et al.) (Docket ID: EPA-HQ-OPP-2019-0305-0056)

Comment: CCQC, USDA, Imazalil Task Force, University of California, Cecelia Packing Co., Haury Inc., Sun Pacific, Johnston Farms, and FGS et al. described the benefits and usage of products containing imazalil, especially in relation to the citrus industry in California, in comparison to other pesticides registered for post-harvest use on citrus fruits. The commenters highlighted imazalil's anti-sporulant and curative properties, for export needs and as a resistance management tool. CCQC and Imazalil Task Force also suggested potential refinements to the risk assessments based on a survey conducted by CCQC. In particular, CCQC and Imazalil Task Force provided new information regarding the number of mixers/loaders nationally, the typical application rates, and the average career length for a mixer/loader. The Imazalil Task Force also committed to perform a "triple pack" of dermal absorption studies and requested that EPA hold the Interim Decision for Imazalil until these new, more accurate studies may be completed. Finally, all commenters commented on EPA's proposal in the PID to require closed systems for applications to citrus fruits. The commenters are unaware of any closed system that could be easily adapted to citrus packing houses and expressed concern that this mitigation would have major financial impacts, especially on smaller packinghouses.

EPA Response: EPA appreciates the new benefits information and considered it in this decision. The Agency used the information provided to refine the risk estimates in the revised risk assessment. Occupational handler and post-application occupational risk estimates for conventional uses were reduced and are no longer of concern. Due to this, the Agency no longer intends to include engineering controls (closed systems for citrus fruit applications) for conventional uses as a mitigation measure. For more information, see *Imazalil: Updated Occupational Handler and Post Application Risk Estimates Re-evaluating Post-Harvest Treatment Equipment to Support Registration Review* or Sections III.A.1.a. and IV.A.

The Agency received and reviewed the dermal absorption studies submitted after the PID. These studies did not change the dermal absorption factor used in the Agency's risk assessment. Lastly,

EPA has considered the commenters' concerns over the closed mixing/loading systems. After additional refinements and characterization described in Sections III. C. and IV. A. of this document, EPA is no longer requiring closed mixing/loading systems.

Comment Submitted by United States Department of Agriculture (USDA) (Docket ID: EPA-HQ-OPP-2013-0305-0049)

Comment: The USDA expressed their support for mitigation outlined in the PID to address risks from antimicrobial uses of imazalil. Their agency provided information on imazalil's efficacy against fungi and gram-positive bacteria. USDA also agreed with EPA's "no effect" determination for listed endangered species due to a lack of environmental exposure. USDA applauded the efforts of EPA and registrants to come to an agreement on mitigation which is effective in reducing risk yet aligns with current industry practices.

EPA Response: The Agency thanks USDA for its support of mitigation to reduce occupational risk from poultry hatchery facilities. EPA appreciates the additional benefits information to further bolster the proposed mitigation, especially regarding the efficacy of imazalil as a fungicide via smoke candle application as well as the description of other efficacy studies in support of the continued use of this active ingredient.

Comments Submitted by Environmental Working Group (EWG) (Docket ID: EPA-HQ-OPP-2013-0305-0047)

Comment: EWG commented on three main points: tolerance levels, endocrine-disruption, and the Food Quality Protection Act (FQPA) Safety Factor. EWG suggested that EPA use a cancer-risk based endpoint, rather than a non-cancer endpoint, for defining the reference dose to set imazalil tolerances. EWG also recommended that EPA review the impacts imazalil may have on the endocrine system, especially for developmental effects. Lastly, EWG requested that EPA reconsider the reduction of the 10x FQPA Safety Factor to 1x.

EPA Response: In this ID, the EPA is making no human health or environmental safety findings associated with the Endocrine Disrupter Screening Program (EDSP) screening of imazalil. Before completing this registration review, the Agency will make an EDSP FFDCA § 408(p) determination. The Agency determined that the 10x FQPA Safety Factor could be reduced to 1x based on consideration of all the available toxicity studies for imazalil including those that evaluate the potential for susceptibility of infants and children. Tolerances are established for the purpose of enforcement and are based on the use pattern specified on the pesticide label, specifically the maximum application rate and minimum re-treatment intervals. Based on the Agency's risk assessment for imazalil, no additional mitigation for dietary risk has been deemed necessary.

II. USE AND USAGE

Imazalil and imazalil sulfate are systemic imidazole fungicides with both conventional and antimicrobial uses. There are no registered residential uses. Imazalil and its sulfate salt are used

in formulations that include liquid soluble concentrate, emulsifiable concentrate, soluble granule, and water-soluble granule, for postharvest treatment of citrus fruits. It can be applied for this use by drenching, dipping, spraying, waxing and foaming equipment. Products containing imazalil are used in rotation with several other pesticides for postharvest treatment. Imazalil is one of two fungicides (fludioxonil is the other) with products registered for this use that has antisporulant activity. Due to this, products containing imazalil are used frequently in postharvest treatment of citrus fruit. For more details, refer to *Use, Usage, Benefits, and Impact of Potential Mitigation on Imazalil (PC# 111901) and Imazalil Sulfate (PC# 111902) Post-harvest Treatment of Citrus*, dated June 28, 2019, which is available in the public docket.

The registrant provided new data since the PID was published which show that occupational handlers handle an average of 2,210 lbs active ingredient (ai) per person per year (the amount handled ranges from 357 to 8,075 lbs ai per person per year, and the median is 592 lbs ai per person per year). EPA used this information to refine the occupational and post-application risk assessments as detailed in Section III.A.1.a. For more details, refer to *Imazalil and Imazalil Sulfate Usage in Citrus Packing Houses in California*, which is available in the public docket.

Products containing imazalil are also used as antimicrobial pesticides to disinfect poultry hatchery facility walls, floors, and equipment prior to introduction of eggs. Imazalil is formulated for this use as an emulsifiable concentrate and as a smoke generator. The emulsifiable concentrate products are applied as dilute sprays using backpack and mechanically pressurized hand-wand sprayers or hand-held foggers, while the smoke generator product is applied by igniting the wick of the canister.

III. SCIENTIFIC ASSESSMENTS

A. Human Health Risks

A summary of the Agency's human health risk assessment is presented below. The Agency used the most current science policies and risk assessment methodologies to prepare a risk assessment in support of the registration review of imazalil and imazalil sulfate. For additional details on the human health assessment for imazalil and imazalil sulfate, see the *Imazalil and Imazalil Sulfate Human Health Draft Risk Assessment for Registration Review*, *Imazalil and Imazalil Sulfate: Addendum to the Human Health Draft Risk Assessment for Registration Review*, and the *Imazalil: Updated Occupational Handler and Post Application Risk Estimates Re-evaluating Post-Harvest Treatment Equipment to Support Registration Review,* which is available in the public docket.

1. Risk Summary and Characterization

a. Conventional Uses

Dietary (Food + Water) Risks

Dietary exposures are only anticipated to result from the conventional uses because the antimicrobial use (hatcheries) is a nonfood use.

The acute dietary exposure assessment is unrefined. It is based on the established tolerances and the assumption that 100% of all citrus and imported banana commodities consumed will be treated with imazalil. The risk estimate for females 13-49, the only subgroup with an acute dietary endpoint, is 56% of the acute population adjusted dose (aPAD), at the 95th percentile of exposure.

The chronic and cancer dietary exposure assessments were refined with the use of the United States Department of Agriculture's (USDA's) Pesticide Data Program (PDP) monitoring data for citrus commodities and bananas (except citrus oil, orange peel, and lemon peel, for which the tolerances were used). The Agency adjusted the data for the presence of a metabolite of concern. The assessments also include anticipated residues in livestock commodities resulting from livestock consumption of citrus pulp. In the chronic assessment, all population subgroups use less than 1% of the chronic population adjusted dose (cPAD).

A dermal point-of-departure (POD) was not selected in the 2018 DRA as imazalil is corrosive and no systemic toxicity was observed at non-corrosive doses tested in the dermal toxicity study. Therefore, it was not necessary to consider systemic toxicity above a corrosive dose. Although a non-cancer dermal POD was not selected, dermal exposure was considered in the cancer risk assessment by converting the oral doses to dermal equivalent doses using a dermal absorption factor (DAF) of 48% to estimate dermal cancer risk estimates. New dermal studies received since the publication of the PID have not changed the DAF. For additional information, refer to *Imazalil and Imazalil Sulfate: Addendum to the Human Health Draft Risk Assessment for Registration Review* and *Imazalil and Imazalil Sulfate: Data Evaluation Records for Dermal Absorption Triple Pack Studies*, which are available in the docket.

Imazalil is classified as "likely to be carcinogenic to humans." A linear low dose approach (Q_1*) was used for quantification of human cancer risk. A cancer potency factor of 6.1×10^{-2} $(mg/kg/day)^{-1}$ was estimated based on the most potent liver tumors in mice and was used to estimate the potential cancer risks of imazalil. Imazalil was not mutagenic in both *in vivo* and *in vitro* mutagenicity assays.

The adult population subgroup with the highest cancer risk estimate is adults 50-99. The cancer risk estimate for this subgroup is 2×10^{-6}. The registrant submitted a comment about using 0 ppm for non-detect residues from monitoring data in the risk assessment, instead of half the limit of detection (LOD). The Agency performed a dietary exposure assessment using a residue value of 0 ppm for orange juice samples that did not have detectable residues and further translated the 0 ppm residue assumption to all citrus juices. With these assumptions, the risk estimate for adults 50-99 decreased slightly, but the cancer risk estimate remains in the range of 2×10^{-6}. These cancer risk estimates are not of concern.

Residential Handler Risks, Residential Post-Application Risks, Bystander Risks, and Aggregate Risks

There are no registered residential uses associated with imazalil or the sulfate salt that could result in exposure in residential settings, so a residential exposure assessment was not performed and there are no residential handler or post-application risks.

Since the applications are made within warehouses, processing plants, and hatchery facilities, spray drift is not anticipated. A quantitative spray drift assessment is not required for imazalil or imazalil sulfate.

The acute aggregate risk estimates are equivalent to the acute dietary risk estimates and are not of concern. The short- and intermediate-term aggregate risks are equivalent to the chronic dietary exposure and risk, which are not of concern. Furthermore, the cancer aggregate risk estimate is equivalent to the cancer dietary exposure and risk estimate of 2×10^{-6} and is not of concern.

Cumulative Risks

The EPA has not made a common mechanism of toxicity to humans finding as to imazalil and any other substance and it does not appear to produce a toxic metabolite produced by other substances. Therefore, the EPA has not assumed that imazalil has a common mechanism of toxicity with other substances for this assessment.

Occupational Handler Risks

Occupational Handler Non-Cancer Risk for Post-Harvest Citrus Applications

A dermal assessment was not conducted in the 2018 DRA because no systemic toxicity was observed at non-corrosive doses tested in the dermal toxicity test; therefore, no dermal hazard is expected. Occupational handler scenarios for imazalil resulted in margins of exposure (MOEs) greater than the inhalation level of concern (LOC) with baseline attire (*i.e.*, no respirator) or engineering controls for automated closed system post-harvest treatments. Inhalation MOEs range from 440 to 19,000,000 (LOC = 30) and are not of concern. These MOEs have not changed since the 2018 DRA.

Since the PID, EPA received and reviewed new dermal absorption studies. These studies did not change the dermal absorption factor used in the Agency's risk assessment.

Occupational Handler Cancer Risk for Post-Harvest Citrus Applications

Since the DRA was issued in 2018, the Agency has received new information including: (1) updated assumptions for amount treated by individual handlers, and (2) revised sub-setting of post-harvest treatment unit exposure data by system type (either dip tank or inline spray/drip/foam systems) and the revised worker inhalation unit exposures in combination with the ambient monitoring for sorters and packers. In the 2018 assessment, EPA did not have information regarding typical rates for post-harvest treatment; therefore, maximum application rates were used to estimate cancer risks. The Agency has received new annual usage data that were used to determine how much active ingredient is used on average to treat a pound of commodity. This resulted in a revised application rate of 2,210 lbs ai per year. In the 2018 risk assessment, the Agency assumed that 100% of the citrus crop was treated and that commercial applicators would be exposed for 100 days per year. For the cancer assessment, a dermal absorption factor of 48% was used to convert oral doses to dermal equivalent doses based on a dermal absorption study. Dermal exposure is the major contributor to the cancer risks.

In the 2018 assessment, commercial post-harvest handler cancer risk estimates ranged from 4 x 10^{-7} to 5 x 10^{-2} using baseline attire, gloves and respirator. When engineering controls (closed mixing/loading systems) were used, these cancer risk estimates ranged from 8 x 10^{-8} to 1 x 10^{-4}. Incorporation of the new information described above resulted in refined commercial handler cancer risk estimates. These refinements resulted in commercial post-harvest handler cancer risk estimates using baseline attire (long-sleeved shirt, long pants, socks and shoes) and gloves ranging from 4 x 10^{-5} to 7 x 10^{-5}. When using a double layer of clothing, gloves and a respirator, cancer risk estimates ranged from 3 x10^{-5} to 4 x 10^{-5}. Commercial handlers using engineering controls resulted in risk estimates ranging from 1 x 10^{-5} to 9 x 10^{-6}. The registered labels do not currently require automated closed systems for mixing and loading. Based on these changes, the Agency determined additional personal protective equipment (PPE) is no longer needed.

Occupational Post-Application Risks

Non-Cancer Post-Harvest Risk For Citrus

There are no occupational post-application non-cancer risk estimates of concern associated with conventional uses of imazalil. All post-application exposure scenarios resulted in MOEs greater than the inhalation LOC (LOC = 30). In the 2018 assessment, the post-application inhalation MOEs for sorters and packers ranged from 320 to 7,000 depending on proximity to the application site.

Since the 2018 assessment, the Agency has revisited the ortho-phenyl-phenol (O-PP) study used in the *Assessment of Occupational Exposure for Post-Harvest Commodity Pesticide Treatments* (February 2018) which included data from six facilities (three pear packinghouses and three citrus facilities). All three pear packing houses used the dip tank system treatments and all three citrus facilities used an inline spray/drip/foam system. New usage information indicated that citrus fruit is no longer dipped for tank treatments but rather spray/foam/drip conveyor belt type systems. Therefore, the Agency has revised risk estimates for workers performing sorting and packing activities.

Ambient air monitoring was conducted in this study and was used previously in the 2018 assessment to assess "indirect" inhalation exposure assessments. EPA has revised the sorter and packer inhalation exposures in combination with the ambient monitoring, as though the ambient monitoring represented individual workers, which is more representative of actual use. Thus, the ambient air data were combined with the individual sorter and packer inhalation monitoring datasets. As all of the ambient air monitoring was conducted in facilities utilizing inline spray/drip/foam systems, the data will be combined with the sorter and packer datasets for that equipment only.

Using the refined inhalation post-application post-harvest treatment system-specific unit exposures for sorters and packers, inhalation post-application non-cancer exposure and risk estimates are not of concern (LOC= 30). Non-cancer inhalation MOEs ranged from 460 to 330,000.

Cancer Post-Harvest Risk For Citrus

In the 2018 assessment, combined (dermal + inhalation) commercial post-application cancer risk estimates ranged from 6 x 10^{-6} for workers not involved in post-harvest treatments to 3 x 10^{-4} for packers and sorters wearing single layer clothing, gloves and no respirator, which is expected based on current food safety laws.

The Agency also assessed whether cancer risk would be reduced by the requirement that packers and sorters use respirators in the 2018 assessment. Use of respirators resulted in cancer risk estimates ranging from 2 x 10^{-4} to 1 x 10^{-6}. As dermal exposure is the major source of the cancer risk, the use of a respirator, which does not reduce dermal exposure, does not reduce the cancer risk significantly.

Since the 2018 assessment, the Agency has reassessed commercial post-application cancer risk estimates for sorters and packers using the new usage information previously described. Risk estimates ranged from 3 x 10^{-4} to 9 x 10^{-6} for workers wearing single layer clothing and gloves. The addition of respirators resulted in refined cancer risk estimates ranging from 3 x 10^{-4} to 8 x 10^{-6}.

b. Antimicrobial Uses

Dietary (Food + Water) Risks

Dietary exposures are not anticipated to result from the use of imazalil in hatcheries; therefore, no dietary risks have been identified. Hatcheries are listed as a nonfood use in the Antimicrobial Pesticide Use Site Index.[1]

Residential Handler Risks and Residential Post-Application Risks

There are no registered antimicrobial uses of imazalil in residential settings; therefore, there are no residential handler or post-application risks.

Occupational Handler Risks

Occupational Handler Non-Cancer Risk for Hatchery Applications

A dermal assessment was not conducted because no systemic toxicity was observed at non-corrosive doses tested in the dermal toxicity test; therefore, no dermal hazard is expected. An inhalation assessment was conducted for a product containing 14.4% ai assuming 26 gallons of product per day would be applied, which is sufficient to treat one million cubic feet of interior volume and is based on the labeled rate. The occupational handler inhalation MOEs range from 280 for the handheld fogger to 83,000 for the backpack sprayer when assessed without respiratory protection. There are no non-cancer risks of concern associated with occupational handler exposure to imazalil as all MOEs are above the inhalation LOC of 30.

[1] The Antimicrobial Pesticide Use Site Index is accessible at: https://www.epa.gov/sites/production/files/2016-10/documents/158w-usi.pdf.

Occupational Handler Cancer Risk for Hatchery Applications

The occupational handler inhalation cancer risks were calculated using the same assumptions as for non-cancer risk along with the assumptions of 52 days per year of exposure (based on weekly applications) and a working lifetime of 35 years out of a 78-year lifespan. In addition, dermal doses were calculated and added to the daily inhalation dose to yield the lifetime average daily dose (LADD). It was also assumed the handler is not wearing a respirator because there is a product with spray and fog applications that does not include this PPE on the label. Cancer risks range from 2×10^{-5} for backpack sprayers to 2×10^{-4} for handheld foggers when assessed without a respirator.

Because dermal exposure is the major source of the cancer risk, the use of a respirator does not reduce dermal exposure; however, the addition of a PF10 respirator (elastomeric half mask respirator) does decrease the cancer risk for applicators using handheld foggers, as it reduces the inhalation daily dose for this application method. With a PF10 respirator, cancer risks remain at 2×10^{-5} for handlers using a backpack sprayer or a mechanically-pressurized handwand sprayer; however, adding a respirator decreases the cancer risk for workers using a handheld fogger from 2×10^{-4} to 4×10^{-5}.

Occupational Post-application Risks

Occupational Post-application Non-cancer Risk for Hatchery Applications

The estimated air concentrations were calculated at various time intervals and used to evaluate the non-cancer risks for imazalil 1) at time zero immediately after application; 2) after the 120-minute restricted entry interval (REI); and 3) as an 8-hour time weighted average (TWA) for a worker who is in a treated space after the REI. The inhalation MOE for the smoke application is 3 when the ventilation rate is 0.5 air changes per hour (ACH) as specified on the label and is of concern because it is below the LOC of 30. EPA calculated the ventilation rate for smoke application that achieves an MOE that is not of concern, which is 1.3 ACH. The MOE for the fog application is 230 when the ventilation rate is 0.5 ACH and is not of concern.

Occupational Post-application Cancer Risk for Hatchery Applications

The 8-hour TWAs for air concentrations for non-cancer risks were used to calculate cancer risks by assuming the exposures occurred 52 times per year for 35 years out of a 78-year lifetime. The combined cancer risk (inhalation and dermal) for the smoke application is 2×10^{-2} when the ventilation rate is 0.5 ACH and 2×10^{-4} for the fog application when the ventilation rate is 0.5 ACH. When higher ACH are used as inputs, the cancer risk is reduced to 1×10^{-4} for the smoke application (at 2.30 ACH) and fog application (at 0.65 ACH). After the DRA published, EPA calculated that a further reduction in cancer risk for smoke and fogging applications (1×10^{-6}) would result from higher ventilation rates of 4.30 ACH and 2.30 ACH, respectively.

2. Human Incidents and Epidemiology

a. Conventional Post-Harvest Uses

Imazalil and imazalil sulfate incidents were previously reviewed in 2013 (S. Recore and E. Evans, D412205, 07/25/13). At that time, based on the low severity and frequency of cases reported to both Incident Data System (IDS) and NIOSH Sentinel Event Notification System for Occupational Risk (SENSOR)-Pesticides, there was not a risk of concern that warranted further analysis.

In the current IDS analysis from January 1, 2013 to February 27, 2018, two cases involving a single active ingredient and one case involving multiple active ingredients were reported to Main IDS; there was one case reported to Aggregate IDS. A query of SENSOR-Pesticides 1998-2014 identified a total of four cases involving imazalil: two cases involved agricultural workers and two cases were non-occupational exposures. In both agricultural-worker cases, workers were exposed while conducting routine fieldwork in citrus orchards.[2] They reported dermal exposure and symptoms including: allergic skin reactions, redness of the skin, and skin rashes. Both of the non-occupational case reports involved the case having allergic or symptomatic reactions after eating fruit.

The Agricultural Health Study (AHS) is a federally-funded study that evaluates associations between pesticide exposures and cancer and other health outcomes and represents a collaborative effort between the US National Cancer Institute (NCI), National Institute of Environmental Health Sciences (NIEHS), CDC's National Institute of Occupational Safety and Health (NIOSH), and the US EPA. Imazalil and imazalil sulfate are not included in the AHS, and therefore this study does not provide information for this report.

Based on the continued low frequency of imazalil and imazalil sulfate incidents reported to both IDS and SENSOR-Pesticides, there does not appear to be a concern at this time. The Agency will continue to monitor the incident data and if a concern is triggered, additional analysis will be conducted.

b. Antimicrobial Uses

There are two incidents for the antimicrobial uses included in the IDS system that occurred from January 1, 2013 to June 22, 2018. Both incidents involve the application of a smoke candle product to hatcheries. In one case, the applications were made to occupied areas, which is in violation of the label instructions, and the worker experienced a dry cough. In the other case, a worker experienced symptoms of bronchitis and lung congestion following previous applications; however, it is not known if the label instructions were followed. In both cases, it is also not known if the respiratory symptoms were caused by exposure to imazalil or if they were caused by the combustion by-products of the smoke candle.

[2] Outdoor imazalil uses on citrus are no longer registered.

The Agency will continue to monitor the incident information. Additional analyses will be conducted if ongoing human incident monitoring indicates a concern.

3. Tolerances

Tolerances for residues of imazalil are established in 40 CFR §180.413.

Codex has established a maximum residue limit (MRL) of 5 ppm for the post-harvest treatment of citrus fruit, and Canada has an MRL of 5 ppm for citrus fruit. The U.S. tolerance for citrus fruit is 10.0 ppm. Codex has established an MRL of 2 ppm for bananas, whereas the U.S. has established a tolerance of 3.0 ppm for bananas. The Codex and Canadian MRLs for citrus fruit and bananas are not harmonized with the U.S. tolerances for these commodities. The U.S. tolerances are established for the combined residues of parent imazalil and its metabolite R014821, whereas the Codex and Canadian MRLs are established in terms of parent imazalil only. The U.S. tolerances cannot be harmonized with the Codex or Canadian MRLs because of the differences in residue definitions and because the U.S. tolerances are higher. If the U.S. tolerances were lowered, over-tolerance residues might result, even though the commodities are treated at the labeled application rates. The Mexican MRLs are based on the U.S. tolerances and, therefore, are harmonized. Codex and Canada have not established tolerances for livestock commodities, and the Mexican MRLs are equivalent to the U.S. tolerances.

4. Human Health Data Needs

No additional data are required to support this registration review decision. The Agency may determine that additional data are needed in the future.

B. Ecological Risks

A summary of the Agency's ecological risk assessment is presented below. The Agency used the most current science policies and risk assessment methodologies to prepare a risk assessment in support of the registration review of imazalil. For additional details on the ecological assessment for imazalil, see the *Imazalil and Imazalil Sulfate: Preliminary Ecological Risk Assessment for Registration Review*, which is available in the public docket.

1. Risk Summary and Characterization – Conventional and Antimicrobial Uses

As stated in the DRA, the registrants are no longer supporting the terrestrial feed crop (barley, wheat, and triticale seed treatment) uses and the greenhouse fogger (bedding plants, cut flowers, flowering plants (baskets and hanging), foliage, ornamentals, and perennials) uses. These labels are in the process of being cancelled (see letter from the Imazalil Task Force to M. Hathaway, dated October 25, 2017). Therefore, only the indoor food (post-harvest citrus fruit treatment) use and antimicrobial uses were considered in the DRA.

Only indoor uses are registered for imazalil and imazalil sulfate; therefore, no outdoor terrestrial exposures are expected. There are no risks of concern for terrestrial taxa, including pollinators.

Aquatic exposure may occur from two potential exposure routes of the discharged water after use in citrus packing houses: (1) to holding/percolation ponds, and (2) to wastewater treatment facilities. Products for use on post-harvest citrus include a label statement that requires a National Pollutant Discharge Elimination System (NPDES) permit for any discharge into waterbodies, thus ensuring low aquatic exposure. In addition, to address potential exposures after discharge to wastewater treatment facilities, an aerobic sewage treatment study was submitted to the Agency. The study demonstrated that imazalil will be biodegraded in aerobic flow-through activated sludge units with a half-life value of about 10 days, so the discharge of the treated water following the wastewater treatment should not be a concern. The Agency does not anticipate any potential ecological risks of concern from the uses of imazalil and imazalil sulfate as a post-harvest citrus fruit treatment.

There are currently three products registered with antimicrobial uses (EPA Reg. numbers: 53883-327, 773-55, and 773-56). These registrations are all for fogging or spraying of poultry and turkey hatchery equipment. Based on the use pattern, no environmental exposure is expected, and, therefore, no adverse ecological effects are anticipated from antimicrobial uses of imazalil.

Given the indoor hatchery uses of imazalil or imazalil sulfate, exposure and potential direct or indirect adverse effects to listed species are not expected to occur. No adverse modification of critical habitat is expected from the use of imazalil and imazalil sulfate. The EPA has made a "no effect" determination under the Endangered Species Act (ESA) for all listed species and designated critical habitat for such species and has therefore concluded that consultation with the U.S. Fish and Wildlife Service and the National Marine Fisheries Service under ESA § 7(a)(2) is not required.

2. Ecological Incidents

A review of the Office of Pesticide Programs Incident Database System (OPP IDS) for both individually reported incidents and aggregate incident reports was completed on May 15, 2018 and reflects reports since its registration. No ecological incidents were identified for imazalil or imazalil sulfate.

The Agency will continue to monitor ecological incident information as it is reported to the Agency. Detailed analyses of these incidents are conducted if reported information indicates concerns for risk to non-target organisms.

3. Ecological and Environmental Fate Data Needs

There are currently no ecological or environmental fate data needs for this registration review. The Agency may determine additional data are needed in the future.

C. Benefits Assessment

1. Conventional Uses

Products containing imazalil and other fungicides such as azoxystrobin, fludioxonil, natamycin, propiconazole, pyrimethanil, sodium orthophenylphenate (*SOPP*), and thiabendazole are available for controlling citrus fruit decay in storage and shipping. Typically, each fruit is treated with one or more fungicides either mixed into or applied before a wax coating when being packed for shipping. Fruits that may be stored (i.e. citrus with low sugar content such as lemons) have an additional application of one or more fungicides either mixed into or applied before a wax coating. Among the registered fungicides, only products containing imazalil and fludioxonil have high efficacy and anti-sporulation properties against green mold on citrus fruits. Using a post-harvest fungicide that has anti-sporulation properties can halt or reduce the spread of the disease through an entire shipment of citrus. As mentioned previously, multiple fungicides are used to treat citrus fruits to control wide spectrum of fungal decay caused by different fungi and to manage resistance in fungi.

A large percentage of harvested citrus fruits may be lost to decay while in storage if not treated with post-harvest fungicides. This situation is unlikely to occur at present, because the application of one or more post-harvest treatments with fungicides is the standard practice in the industry. According to citrus industry experts, removing a single active ingredient may not be immediately detrimental to the citrus industry; however, impacts are expected over an extended time-period due to development of resistance.

Additionally, many countries have established import tolerances for products containing imazalil. Exports of citrus fruits must meet the pesticide regulations of an importing country. Most countries accept fruits treated with products containing imazalil, fludioxonil, and thiabendazole; however, many countries do not have established tolerances for newer active ingredients registered for postharvest citrus use and, therefore, cannot accept fruit treated with these active ingredients. This limits the pest control options for citrus fruits bound for export markets.

For additional details on the benefits assessment for imazalil, please refer to *Use, Usage, Benefits, and Impact of Potential Mitigation on Imazalil (PC# 111901) and Imazalil Sulfate (PC# 111902) Post-harvest Treatment of Citrus*, dated June 28, 2019, which is available in the public docket.

2. Antimicrobial Uses

Imazalil is used in commercial poultry hatcheries to prevent fungi (primarily *Aspergillus fumigatus*) prior to the introduction of eggs. An outbreak of *A. fumigatus* impacts the viability of chicks by increasing morbidity from fungal respiratory diseases (aspergilloses). Once poultry stock becomes infected, there are no effective treatments against aspergillosis.[3] The source of the fungus likely results from contamination due to poultry breeding operations, to the point where it

[3] Arne et al. (2011). Aspergillus fumigatus in Poultry. International Journal of Microbiology. Vol. 2011, Article ID 746356. 14 pp.

is generally recommended that hatchery workers not be employed simultaneously in poultry processing plants, markets, or in poultry-raising or -handling operations.[4] *Aspergillus* fungi are ubiquitous and can exist even in difficult environmental conditions, thus the purpose of imazalil products is to prevent contamination of eggs in hatchery facilities rather than to treat an existing fungal outbreak. Without a frequent and consistent sanitary protocol for facilities and equipment, hatcheries are at risk of contamination due to the prevalence of *Aspergillus* spp. In those cases, facilities would experience decreased hatching rates and increased chick mortality resulting in significant economic losses, as well as the added expense of treating an outbreak.[5]

There are numerous chemicals registered for use in hatcheries at different stages of egg hatching and chick rearing. Imazalil is used as a fogger and hard-surface treatment for equipment, floors, and walls prior to egg introduction. Alternative chemicals include formaldehyde (Case 0556); sodium chloride (part of the inorganic halides case, Case 4051); chlorine dioxide (Case 4023); hydrogen peroxide, peroxyacetic acid, and potassium peroxymonosulfate (all three part of peroxy compounds, Case 4072); alkyldimethylbenzylammonium chloride (ADBAC, Case 0350); didecyldimethylammonium chloride (DDAC, Case 3003); iodine and iodophors (Case 3080); multiple phenolic compounds such as para-tertiary-Amylphenol (PTAP) and ortho-phenyl phenol (O-PP, Case 2575); and glutaraldehyde (Case 2315). It is anticipated that hatcheries use a combination of these registered chemicals in addition to imazalil to prevent outbreaks of other microorganisms beyond fungi.

All of the alternatives can be used as broad-spectrum disinfectants, bacteriocides and fungicides and are used in a wide variety of use sites, whereas imazalil's only antimicrobial use is as a hatchery fungicide. While the use of imazalil is narrow, its presence in the marketplace offers another option to hatcheries and decreases the chance of pathogen resistance. For this specific use site, alternatives to imazalil are anticipated to have similar, negligible environmental exposures and therefore no ecological risks are expected.

On an active ingredient level, there have been two human health incidents known to the Agency from potential exposure to antimicrobial uses of imazalil, compared to the nearly 2,337 incidents associated with exposure to quaternary ammonium compounds (such as ADBAC and DDAC) for the period spanning 2006-2017 alone. These incidents reported dermal, ocular, and inhalation irritation, with eye symptoms most commonly reported as associated with exposure to quaternary ammonium compounds. Within a similar timeframe, 232 incidents were reported for O-PP disinfectants, with several major incidents relating to respiratory distress. For the peroxy compounds case as a whole, 98 incidents have been reported (though none for potassium peroxymonosulfate or peroxyacetic acid). These included dermal, ocular, and inhalation effects. Iodine and iodophors, chlorine dioxide, formaldehyde, and glutaraldehyde by comparison have far fewer incidents reported over a similar time period (21, 12, 8, and 4 incidents respectively). There have been no incidents reported associated with the use of sodium chloride or PTAP. It should be noted that because imazalil's alternatives are used by a greater number of end users due to their broad applications in residential settings and public access areas, there is an

[4] Samberg Y. and M. Meroz (1995). Application of Disinfectants in Poultry Hatcheries. Revue scientifique et technique (International Office of Epizootics). Vol. 14, issue 2. 15 pp.
[5] Intervet International B.V. (2010). Aspergillus Control in Hatcheries with Clinafarm. 30 pp.

increased potential for accidents or misuse of those products. Imazalil, by contrast, is used in a very specific and controlled manner with required personal protective equipment and facility controls.

While acute mammalian toxicity studies are not a substitute for subchronic and chronic toxicity data, they do provide some insight into how imazalil compares to its alternatives and may explain some of the incidents noted above. Imazalil is considered moderately toxic by the oral route (Toxicity Category II) and a severe eye irritant (I) but is rated either III or IV for all other categories. It is not a dermal sensitizer. In examining toxicity profiles, the following are classified as severe eye and skin irritants (I): formaldehyde, glutaraldehyde, peroxy compounds, phenolic compounds (no eye irritation study is available for O-PP), ADBAC and DDAC. Additionally, both formaldehyde and glutaraldehyde are dermal sensitizers. Iodine is a severe skin irritant and has high oral toxicity. The acute toxicity of chlorine dioxide is considered significant by the oral route (II). Hydrogen peroxide and peroxyacetic acid are moderately irritating to the lungs (II) while potassium peroxymonosulfate is of low acute inhalation toxicity (IV). No data are available for eye irritation for either chlorine dioxide or iodine. Sodium chloride is classified as either III or IV for all Toxicity Categories. This information suggests imazalil has a slightly more favorable acute toxicity profile compared to its alternatives (with the exception of sodium chloride).

Table 1: Acute Toxicity Category Profiles of Imazalil and its Alternatives [A]

Chemical Case (Case Number)	Acute Oral	Acute Dermal	Acute Inhalation	Dermal Irritation	Eye Irritation	Dermal Sensitization
Imazalil (Case 2325)	II	III	IV	IV	I	N
Peroxy Compounds (Case 4072)	III	II/III [B]	II/IV [C]	I	I	Waived
Iodine and Iodophors (Case 3080)	II	III	II	I	Unknown [D]	N
Sodium Chloride (Inorganic Halides, Case 4051)	III	Waived	Waived	IV	III	Waived
Formaldehyde (Case 0556)	II	II	II	I	I	Y
Glutaraldehyde (Case 2315)	II	III	Unknown [D]	I	I	Y
ADBAC (Case 0350)	II	II	II	I	I	N
DDAC (Case 3003)	II	III	II	I	I	N
Chlorine Dioxide (Case 4023)	II	III	II	II	III	Unknown [D]

O-PP (Case 2575)	III	IV	Unknown [D]	I	Unknown [D]	N
PTAP (Case 3014)	III	III	Unknown [D]	I	I	Unknown [D]

A. Toxicity category definitions: (I) Highly toxic or severely irritating; (II) Moderately toxic or moderately irritating; (III) Slightly toxic or slightly irritating; (IV) Practically non-toxic or not an irritant.
B. Peroxyacetic acid is more acutely toxic via the dermal route (II) than hydrogen peroxide and potassium peroxymonosulfate (III).
C. Hydrogen peroxide and peroxyacetic acid are moderately irritating to the lungs (Tox Category II) while potassium peroxymonosulfate is of low acute inhalation toxicity (IV)
D. No acceptable study is available.

IV. INTERIM REGISTRATION REVIEW DECISION

A. Risk Mitigation and Regulatory Rationale

In evaluating potential risk mitigation for imazalil and imazalil sulfate, EPA considered the risks, the benefits, and the use patterns of these compounds. EPA did not find any risks of concern for residential, dietary, bystander, aggregate, or cumulative exposure scenarios. The Agency did not find any ecological risks of concern for any terrestrial taxa, including pollinators, and anticipates no significant aquatic exposure. As indicated in Appendix D, the Agency has made a "no effect" determination under ESA for imazalil and imazalil sulfate uses. The Agency is not making a determination for endocrine effects under the EDSP. In the PID, the Agency proposed risk mitigation measures to reduce the potential for exposure to humans; however, the risk picture has changed due to new use and usage information received during the comment period, as has the mitigation for conventional uses. The changes to the human health risk assessment are described further in Section III.A.1.a. The Agency is no longer requiring engineering controls for conventional uses. The EPA is requiring label changes to address generic labeling requirements for all imazalil products and uses and fungicide resistance management. The registrants are aware of the mitigation measures.

Post-application workers for conventional uses have cancer risks up to 3x 10^{-4} (packers and sorters wearing single layer clothing, gloves, and no respirator). Several factors have been brought to the EPA's attention that characterize this risk. After a product containing a pesticide is applied to the citrus fruit, the fruit is transported directly into a heater to dry the fruit, reducing the likelihood that residue will transfer to packers and sorters. Food safety laws encourage anyone handling fruit to wear gloves, also reducing the potential for dermal contact with imazalil. Additionally, it is estimated that approximately 20,000 people[6,7] are employed in citrus production in the United States. According to the California Citrus Quality Council (CCQC), an estimated 7 percent of these people (approximately 1,400 individuals) are employed as packers and sorters full time and could potentially be exposed to imazalil. The small number of individuals involved in packing and sorting limits the number of people who could potentially

[6] Court et al. (2017). Economic Contributions of the Florida Citrus Industry in 2015-16. University of Florida: Economic Impact Analysis Program.
[7] Babcock B. (2018). Economic Impact of California's Citrus Industry. Citrus Research Board.

experience the lifetime exposure to imazalil assumed in the cancer risk estimates. In addition, the citrus industry is moving away from traditional packing and sorting to more automated systems due to the relatively high cost of labor, which will further reduce the number of people potentially exposed as this trend continues. Based on the conservative assumptions (described in § III) used to estimate cancer risk for post-application workers for conventional uses, as well as the low number of people exposed, the Agency concludes that the cancer risk estimate is not of concern and will not require mitigation for packers and sorters.

For antimicrobial uses, the Agency is requiring additional respiratory protection and increased ventilation rates post-application to mitigate cancer and non-cancer risks from fogging and smoke candle uses. There is no required risk mitigation for spray uses of imazalil as both cancer and non-cancer risks are not of concern; however, there are updated required respiratory protection requirements as outlined in Appendix B.

3. Conventional Uses

a. Fungicide Resistance Management

Pesticide resistance may occur when genetic or behavioral changes enable a portion of a plant pest population (such as bacteria, fungi, insects or other organisms) to tolerate or survive what would otherwise be lethal doses of a pesticide. The surviving pest populations increase with continued exposure to a no longer effective pesticide. Resistance to pesticides by plant pests appears to be increasing in the U.S. and worldwide. Managing the evolution of pesticide resistance in plant pests is an important part of sustainable pest management and an integral part of integrated pest management (IPM) programs, to assist crop producers to manage plant pests effectively.

The development of pesticide resistance is influenced by a number of factors. One important factor that fosters pesticide resistance is the repeated use of pesticides with the same mode of action on the same pest population. Repeated use of a pesticide with a single mode of action kills sensitive pests but allows pests in the population that are tolerant of the pesticide to increase in numbers. These individuals will generally be unaffected by the repeated pesticide applications and may ultimately make-up a substantial portion of the pest population. Thus, an important proactive pesticide resistance-management strategy is to rotate pesticides with different modes of action to increase the likelihood of controlling target pests in any given location or area. This approach may delay and/or prevent the development of resistance to a particular mode of action without resorting to increased rates and frequency of application and may prolong the useful life of pesticides. The EPA is requiring resistance-management labeling, as listed in Appendix B, for products containing the fungicides, imazalil and imazalil sulfate, to provide pesticide users with easy access to important information to help maintain the effectiveness of useful pesticides. Additional information on the EPA's guidance for resistance management can be found at the following website: https://www.epa.gov/pesticide-registration/pesticide-registration-notices-year.

4. Antimicrobial Uses

The Agency is mitigating occupational handler risks posed by antimicrobial uses of imazalil. The mitigation requirements are anticipated to resolve risks and, overall, pose little burden to hatcheries in terms of implementation; however, the Agency anticipates facilities that currently do not have PF50 respirators available may incur high start-up expenses to be in compliance with FIFRA safety standards. The antimicrobial imazalil registrants have agreed to the following changes.

a. Personal Protective Equipment

To mitigate cancer risks of concern for occupational handlers of handheld foggers, the Agency is requiring PF10 (elastomeric half mask) respiratory protection on imazalil labels. The risk of 2×10^{-4} for the handheld fogger scenario is expected to reduce to 4×10^{-5} when PF10 respiratory protection is worn. Updating the respirator requirement for this scenario will reduce cancer risk estimates. The registrant indicated they have been considering increasing respirator requirements prior to this decision document based on the findings of the imazalil DRA. Respirator costs are variable depending upon the protection level desired, disposability, comfort, and the kinds of vapors and particulates being filtered. However, for PF10 respirators, while having variable costs, the annual fit testing may be the majority of the cost.

Currently, the smoke candle label states that workers can safely enter the facility after two hours of ventilation (or 12 hours in an unventilated hatchery). The Agency has determined that workers who must enter the facility prior to the two-hour restricted entry interval (REI) in cases of emergency would not have sufficient PPE because imazalil is an acute toxicity category I for eye irritation. To address this concern, EPA is requiring the use of PF50 (full face mask) respiratory protection for workers who must enter the hatchery prior to the two-hour REI.

EPA anticipates economic impacts to poultry workers or facilities from requiring a PF50 respirator. Respirator requirement costs consist of two parts: the costs of respirator and fit test requirements. PF50 respirator costs are extremely variable depending upon the protection level desired, disposability, comfort, and the kinds of vapors and particulates being filtered. These respirators, while having variable costs, are generally expensive and would have high financial impact on a poultry worker who does not already own one or poultry facilities that need to provide it to their workers.

Additionally, the Agency is requiring updated respiratory protection language for spray uses, as detailed in Appendix B. EPA does not anticipate this requirement will place undue burden on hatchery facilities to comply, as respirators are already required per the labels for spray and fogging uses, and the full-face respirator is only required post-application in the event that a worker needs to reenter the facility for an emergency following the smoke candle use.

b. Ventilation Rates in Hatcheries

While most imazalil labels require one air exchange within two hours prior to reentry (0.5 air changes per hour, or ACH), EPA expects the air exchange rate to be much higher in practical use

because hatcheries are concerned with chick viability, and proper ventilation dissipates chemicals used in disinfection to a level safe for poultry. For reference, a typical office building should have at least 4-10 ACH depending on the occupancy and size of the office. The Agency is requiring several increases in ventilation rates to be included on imazalil labels. The increased rate will mitigate both cancer and non-cancer risks identified for post-application exposure to imazalil. For smoke candle applications, EPA is requiring a ventilation rate of 4.5 ACH (9 air changes over two hours) to reduce the cancer risk from 2×10^{-2} to 1×10^{-6}. This rate also increases the smoke candle MOE above the Agency's level of concern (LOC = 30), reducing the non-cancer inhalation risk. For fogging applications, EPA is requiring an increase in air exchange rate from 0.5 to 2.5 ACH (5 air changes over two hours). This will decrease the cancer risk from 2×10^{-4} to 1×10^{-6}. The registrant believes a higher air exchange rate is already used in hatcheries.

The Agency anticipates that because hatcheries likely use a higher ventilation rate than required on the label, increasing the required ACH will not increase the cost of using imazalil or pose a major burden to hatcheries.

B. Tolerance Actions

The residues of concern in bananas and citrus fruit (40CFR §180.413(a)(1)) for tolerance enforcement are parent imazalil: 1-[2-(2,4-dichloro-phenyl)-2-(2-propenyloxy)ethyl]-1H-imidazole and its metabolite, 1-(2,4-dichlorophenyl)-2-(1H-imidazole-1-yl)-1-ethanol. The Agency anticipates revising the tolerance expression to: "Tolerances are established for residues of the fungicide imazalil, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only imazalil, 1-[2-(2,4-dichloro-phenyl)-2-(2-propen-1-yloxy)ethyl]-1H-imidazole and 1-(2,4- dichlorophenyl)-2-(1H-imidazole-1-yl)-1-ethanol."

The residues of concern in livestock commodities (40CFR §180.413(a)(2)) for tolerance enforcement are parent imazalil, 1-[2-(2,4-dichloro-phenyl)-2-(2-propenyloxy)ethyl]-1H-imidazole, and its metabolites, 3-[2-(2,4-dichlorophenyl)-2-(2,3-dihydroxypropoxy)ethyl]-2,4-imidazolidinedione, and 3-[2-(2,4 dichlorophenyl)-2-hydroxy)]-2,4-imidazolidinedione. The Agency anticipates revising the tolerance expression to: "Tolerances are established for residues of the fungicide imazalil, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only imazalil, 1-[2-(2,4-dichloro-phenyl)-2-(2-propen-1-yloxy)ethyl]-1H-imidazole, 3-[2-(2,4- dichlorophenyl)-2-(2,3-dihydroxypropoxy)ethyl]-2,4-imidazolidinedione, and 3-[2-(2,4- dichlorophenyl)-2-hydroxy)]-2,4-imidazolidinedione."

The 40 CFR listing for imazalil currently gives the chemical name as 1-[2-(2,4-dichloro-phenyl)-2-(2-propenyloxy)ethyl]-1H-imidazole. The Agency anticipates correcting the name to 1-[2-(2,4-dichloro-phenyl)-2-(2-propen-1-yloxy)ethyl]-1H-imidazole.

The Agency anticipates changes to the citrus tolerances due to current guidance concerning rounding classes and significant figures. The revised tolerances are summarized in the table below. Livestock commodity tolerances were originally established as a result of residues in

dried citrus pulp, rather than feed items associated with wheat and barley, so the cancellation of seed treatment uses on wheat and barley did not impact the livestock commodity tolerances. The tolerance for bananas also has not changed. The Agency will use its Federal Food, Drug, and Cosmetic Act (FFDCA) rulemaking authority to pursue tolerance changes.

Table 2: Summary of Anticipated Tolerance Actions

Imazalil40 CFR § 180.413: Summary of Anticipated Tolerance Actions			
Commodity	Established Tolerance (ppm)	Anticipated Tolerance (ppm)	Comments
Citrus, dried pulp	25.0	30	Increase tolerance and delete decimal to conform to rounding classes
Citrus, oil	200.0	200	Delete decimal to conform to rounding classes
Fruit, citrus, postharvest	10.0	Remove	Tolerance will be replaced with tolerance for expanded crop group
Fruit, citrus, group 10-10	None	10	Updated crop group and correct rounding class

EPA has determined that there is no human dietary risk from registered uses of imazalil and imazalil sulfate that is inconsistent with the FFDCA safety standard. Taking into consideration the available information on toxicity and exposure, EPA assessed imazalil and imazalil sulfate's potential aggregate risks, including dietary (food and water) and non-occupational residential exposures, and found no risks exceeding the Agency's levels of concern.

EPA concludes that there is a reasonable certainty that no harm will result from aggregate exposure to imazalil and imazalil sulfate, including all anticipated dietary exposures and all other exposures for which there is reliable information. Therefore, residues of imazalil and imazalil sulfate are safe. EPA intends to leave the modified tolerances in place, as EPA's analysis indicates that such modifications would also be safe.

C. Interim Registration Review Decision

In accordance with 40 CFR §§ 155.56 and 155.58, the Agency is issuing this ID. Except for the EDSP, the Agency has made the following interim decision: (1) no additional data are required; and (2) imazalil does not meet the FIFRA registration standard without the changes to the affected registrations and their labeling as described in Section IV.A and Appendices A and B.

The Agency has conducted detailed draft Human Health and Ecological Risk Assessments. In these risk assessments, EPA has observed a few risks to continuing to register imazalil. Occupational handler and occupational post-application risks of concern from antimicrobial uses of imazalil are addressed by adding PPE and increasing ventilation rates after applications on all antimicrobial product labels. EPA has also determined that continuing to register imazalil provides benefits to the citrus industry as it has high efficacy and anti-sporulation properties against green mold on citrus fruits and plays a significant role in fungicide resistance management. Additionally, imazalil is an important active ingredient in hatchery settings due to its efficacy against *Aspergillus* fungi and bacteria, thus it prevents chick mortality and decreased hatching rates.

During registration review, EPA considers whether a pesticide registration "continues to satisfy the FIFRA standard for registration."[8] EPA has determined that imazalil does not meet the registration standard without changes to the affected registrations and their labeling. EPA finds that the mitigation specified in Sections IV. A-B and Appendices A and B are sufficient to address certain concerns. In this ID, the Agency is making no human health or environmental safety findings associated with the EDSP screening of imazalil (Appendix D). The Agency's final registration review decision for imazalil will be dependent upon an EDSP FFDCA § 408(p) determination. In addition, the Agency has made a "no effect" determination for all listed species and designated critical habitat for such species and has therefore concluded that consultation with the U.S. Fish and Wildlife Service and the National Marine Fisheries Service under ESA § 7(a)(2) is not required (Appendix C).

D. Data Requirements

No additional data are anticipated to be required to support this registration review.

V. NEXT STEPS AND TIMELINE

A. Interim Registration Review Decision

A Federal Register Notice will announce the availability of this ID for imazalil. A final decision on the imazalil registration review case will occur after an EDSP FFDCA § 408(p) determination.

B. Implementation of Mitigation Measures

Once the Interim Registration Review Decision is issued, the imazalil registrants must submit amended labels that include the label changes described in Appendix B. The revised labels and registration amendments must be submitted to the Agency for review within 60 days following issuance of the Interim Registration Review Decision.

Registrants must submit a cover letter, a completed Application for Registration (EPA form 8570-1) and electronic copies of the amended product labels. Two copies for each label must be submitted, a clean copy and an annotated copy with changes. In order for the application to be processed, registrants must include the following statement on the Application for Registration (EPA form 8570-1):

"I certify that this amendment satisfies the requirements of the imazalil Interim Registration Review Decision and EPA regulations at 40 CFR Section 152.44, and no other changes have been made to the labeling of this product. I understand that it is a violation of 18 U.S.C. Section 1001 to willfully make any false statement to EPA. I further understand that if this amendment is

[8] 140 C.F.R. § 155.40(a). In a PID, EPA sets out a proposed interim decision that includes EPA's "proposed findings with respect to the FIFRA risk-benefit standard for registration and describe the basis for such proposed findings." 40 C.F.R. §§ 155.56, 155.58(b)(1).

found not to satisfy the requirements of the imazalil Interim Registration Review Decision and 40 CFR Section 152.44, this product may be in violation of FIFRA and may be subject to regulatory and/or enforcement action and penalties under FIFRA."

Within the required timeframe, registrants must submit the required documents to the Re-evaluation section of EPA's Pesticide Submission Portal (PSP), which can be accessed through the EPA's Central Data Exchange (CDX) using the following link: https://cdx.epa.gov/. Registrants may instead send paper copies of their amended product labels, with an application for a fast-track, Agency-initiated non-PRIA label amendment to Michelle Nolan (for conventional uses) or to Kimberly Wilson (for antimicrobial uses) at one of the following addresses, so long as the labels and application are submitted within the required timeframe:

For Label Amendments Pertaining to Conventional Products

VIA US Mail
USEPA Office of Pesticide Programs
Pesticide Re-evaluation Division Mail Code 7508P
1200 Pennsylvania Ave NW
Washington, DC 20460-0001

VIA Courier
Pesticide Re-evaluation Division
c/o Front End Processing
Room S-4910, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

For Label Amendments Pertaining to Antimicrobial Products

VIA US Mail
USEPA Office of Pesticide Programs
Antimicrobials Division Mail Code 7510P
1200 Pennsylvania Ave NW
Washington, DC 20460-0001

VIA Courier
Antimicrobials Division
c/o Front End Processing
Room S-4910, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Appendix A: Summary of Actions for Imazalil

Registration Review Case#: 2325
PC Code: 111901 (imazalil), 111902 (imazalil sulfate)
Chemical Type: Fungicide
Chemical Family: Imidazole
Mode of Action: Demethylation inhibitors

Affected Population(s)	Source of Exposure	Route of Exposure	Duration of Exposure	Potential Risk(s) of Concern	Actions
Occupational Post-App - Hatcheries	Smoke candle	Inhalation	Short-, intermediate-, and long-term	Non-cancer inhalation	Increase ventilation rate prior to reentry
Occupational Post-App - Hatcheries	Smoke candle	Eye	Acute	Severe eye irritation	Require increased PPE for early reentry
Occupational Post-App - Hatcheries	Smoke candle	Inhalation, dermal	Lifetime	Cancer	Increase ventilation rate prior to reentry
Occupational Post-App - Hatcheries	Fogging	Inhalation, dermal	Lifetime	Cancer	Increase ventilation rate prior to reentry
Occupational Handlers - Hatcheries	Handheld fogger	Inhalation, dermal	Lifetime	Cancer	Require increased PPE

Appendix B: Labeling Changes for Imazalil Products

Summary of Labeling Changes for Conventional Imazalil Products		
Description	**Label Language for Imazalil Products**	**Placement on Label**
	End Use Products	
Mode of Action Group Number	**Imazalil and Imazalil Sulfate** **GROUP** **3** **FUNGICIDE**	Front Panel, upper right quadrant. All text should be black, bold face and all caps on a white background, except the mode of action code, which should be white, bold face and all caps on a black background; all text and columns should be surrounded by a black rectangle.
Resistance-management for fungicides and bactericides	Include resistance management label language for fungicides/bactericides from PRN 2017-1 (https://www.epa.gov/pesticide-registration/pesticide-registration-notices-year)	Directions for Use, prior to directions for specific crops

Summary of Labeling Changes for Antimicrobial Imazalil Products		
Description	**Label Language for Imazalil Products**	**Placement on Label**
	End Use Products	
Handler Respiratory Protection for Spray Uses in Hatchery Facilities	"Handlers entering the treated area before the ventilation period is over must wear a long-sleeved shirt and long pants, shoes plus socks, chemical-resistant gloves and wear a minimum of a NIOSH-approved respirator with a particulate filtering facepiece respirator with any N*, R, or P filter; OR a NIOSH-approved powered air-purifying respirator with HE filters." *Drop the "N" option if there is oil in the product's formulation and/or the product is labeled for mixing with oil-containing products.	Precautionary Statements -Personal Protective Equipment

Summary of Labeling Changes for Antimicrobial Imazalil Products		
Description	**Label Language for Imazalil Products**	**Placement on Label**
Handler Respiratory Protection for Handheld Fogger Use in Hatchery Facilities	"All handlers must wear long-sleeved shirt and long pants, shoes plus socks, chemical resistant gloves, and chemical resistant apron. Handlers using handheld foggers must wear a minimum of a NIOSH-approved elastomeric half mask respirator with organic vapor (OV) cartridges and combination N*, R, or P filter; OR a NIOSH-approved gas mask with OV canisters; OR a NIOSH-approved powered air-purifying respirator with OV cartridges and combination HE filters." *Drop the "N" option if there is oil in the product's formulation and/or the product is labeled for mixing with oil-containing products.	Precautionary Statements -Personal Protective Equipment
Post-application Respiratory Protection for Smoke Candle Use in Hatchery Facilities	"Handlers entering the treated area before the ventilation period is over must wear a long-sleeved shirt and long pants, shoes plus socks, chemical resistant gloves and wear a minimum of a NIOSH-approved elastomeric half mask respirator with organic vapor (OV) cartridges; OR a NIOSH-approved full face respirator with OV cartridges; OR a gas mask with OV canisters; OR a powered air purifying respirator with OV cartridges." *Drop the "N" option if there is oil in the product's formulation and/or the product is labeled for mixing with oil-containing products.	Precautionary Statements -Personal Protective Equipment
Occupational PPE for Early Reentry Following Smoke Candle Use in Hatcheries	"During early re-entry handlers must wear a long-sleeved shirt, long pants, shoes, socks and chemical resistant gloves and a full-face respirator with a protection factor (PF) of 50."	Precautionary Statements -Personal Protective Equipment
Respirator Fit Testing, Medical Qualification, and Training (all uses)	"Using a program that conforms to OSHA's requirements (see 29 CFR Part 1910.134), employers must verify that any handler who uses a respirator is: • Fit-tested and fit-checked, • Trained, and • Examined by a qualified medical practitioner to ensure physical ability to safely wear the style of respirator to be worn. A qualified medical practitioner is a physician or other licensed health care professional who will evaluate the ability of a worker to wear a respirator. The initial evaluation consists of a questionnaire that asks about medical conditions (such as a heart condition) that would be problematic for respirator use. If concerns	Directions for Use

Summary of Labeling Changes for Antimicrobial Imazalil Products		
Description	**Label Language for Imazalil Products**	**Placement on Label**
	are identified, then additional evaluations, such as a physical exam, might be necessary. The initial evaluation must be done before respirator use begins. Handlers must be reexamined by a qualified medical practitioner if their health status of respirator style or use-conditions change. Upon request by local/state/federal/tribal enforcement personnel, employers must provide documentation demonstrating how they have complied with these requirements."	
Occupational PPE for Handheld Fogger Use in Hatchery Facilities	"When applying imazalil in hatchery facilities using a handheld fogger, a respirator with a protection factor (PF) of 10 is required."	Directions for Use
Increase in Required Air Exchanges Following Fogging in Hatchery Facilities	"Do not reenter the unventilated area for at least 12 hours. For ventilated areas, do not re-enter treated areas for at least 2 hours, provided that at least 5 air exchanges have occurred during that period."	Directions for Use
Increase in Required Air Exchange Following Smoke Candle Use in Hatchery Facilities	"Do not reenter the unventilated area for at least 12 hours. For ventilated areas, do not re-enter treated areas for at least 2 hours, provided that at least 9 air exchanges have occurred during that period."	Directions for Use

Appendix C: Endangered Species Assessment

There is no reasonable expectation for any registered use of imazalil to cause direct or indirect adverse effects to threatened and endangered species. No adverse modification of critical habitat is expected from the use of imazalil. Since there are no outdoor uses of products containing imazalil and imazalil sulfate and the Agency does not expect environmental contamination from indoor uses, the EPA has made a "no effect" determination for all listed species and designated critical habitat for such species and has therefore concluded that consultation with the U.S. Fish and Wildlife Service and the National Marine Fisheries Service under ESA § 7(a)(2) is not required.

Appendix D: Endocrine Disruptor Screening Program

As required by FIFRA and FFDCA, the EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, sub-chronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, the EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its most recent registration decision for imazalil, the EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA § 408(p), imazalil is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

The EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where the EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA § 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, the EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. The Agency has reviewed all of the assay data received for the List 1 chemicals and the conclusions of those reviews are available in the chemical-specific public dockets. A second list of chemicals identified for EDSP screening was published on June 14, 2013,[9] and includes some pesticides scheduled for Registration Review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors. Imazalil is not on either list. For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit the EPA website.[10]

[9] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.
[10] https://www.epa.gov/endocrine-disruption

In this ID, the EPA is making no human health or environmental safety findings associated with the EDSP screening of imazalil. Before completing this registration review, the Agency will make an EDSP FFDCA § 408(p) determination.